Mortality in Individuals Aged 80 and Older with Type 2 Diabetes Mellitus in Relation to Glycosylated Hemoglobin, Blood Pressure, and Total Cholesterol

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OBJECTIVES: To evaluate whether low glycosylated hemoglobin (HbA1c), blood pressure (BP), and total cholesterol (TC) are associated with lower risk of all-cause mortality in very old individuals with type 2 diabetes mellitus.

DESIGN: Population-based cohort study.

SETTING: Primary care database in the United Kingdom.

PARTICIPANTS: Individuals aged 80 and older with type 2 diabetes mellitus (N = 25,966).

MEASUREMENTS: Associations between baseline HbA1c, BP, and TC and all-cause mortality were evaluated in Cox proportional hazards models. Analyses were adjusted for sex, age, duration of diabetes mellitus, lifestyle variables, HbA1c, BP, TC, comorbidities, prescribing of antidiabetic and cardiovascular drugs, and participants' general practice.

RESULTS: There were 4,490 deaths during follow-up (median 2.0 years; mortality 104.7 per 1,000 person-years). Mortality in participants with low (<6.0% (<42 mmol/mol)) or high (≥8.5% (≥69 mmol/mol)) HbA1c was similar to that in those with the reference HbA1c (8.0–8.4% (64–68 mmol/mol)). Mortality was lowest in individuals with HbA1c of 7.0–7.4% (53–57 mmol/mol) (80.9 per 1,000 person-years, adjusted hazard ratio (aHR) = 0.80, 95% confidence interval (CI) = 0.70–0.91, $P = .001$). Mortality was higher in individuals with lower BP (e.g., <130/70 mmHg, 151.7 per 1,000 person-years, aHR = 1.52, 95% CI = 1.34–1.72, $P < .001$ vs reference BP <150/90 mmHg) and in the lowest TC category (<3.0 mmol/L, 138.7 per 1,000 person-years, aHR = 1.42, 95% CI = 1.24–1.64, $P < .001$ vs reference TC 4.5–4.9 mmol/L). The relationship between TC and mortality varied according to sex and prescription of lipid-lowering drugs.

CONCLUSION: Low HbA1c, BP, and TC may be associated with higher mortality in very old adults with type 2 diabetes mellitus. Further research is required to understand these associations and to identify optimal treatment targets in this population. **J Am Geriatr Soc 2016.**

Key words: aged 80 and older; blood pressure; cholesterol; HbA1c; type 2 diabetes mellitus

Recent increases in life expectancy have resulted in increasing numbers of people living to very advanced ages. Very old people (≥80) are an increasingly important group of health services users, often having multiple chronic conditions and requiring multiple medications.[1,2] Type 2 diabetes mellitus has become a particular concern for older people. In the United Kingdom, two-thirds of individuals with diabetes mellitus are aged 60 and older, and 13% are aged 80 and older.[3] Despite the high prevalence of type 2 diabetes mellitus in very old adults, evidence to inform management of individuals aged 80 and older is limited because this older population is seldom included in clinical trials.[4,5] Treatment decisions for older adults may be largely based on professional opinion, drawing on evidence from younger adults but taking into account a range of concerns, such as comorbidities, declining physical and cognitive functioning, and perceptions of life expectancy, which may not be relevant in younger people.[6]

Cardiovascular disease (CVD) is the leading cause of mortality in individuals with diabetes mellitus,[7,8] and clinical guidelines stress the importance of cardiovascular risk reduction by lowering blood glucose, blood pressure (BP), and cholesterol in individuals with diabetes mellitus.[6,9] There is concern that risk factor reduction may not always be optimal. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study found higher mortality in the intensive glucose-lowering group.[10] Additional evidence

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has emerged from observational studies that risk of mortality is greater with low glycosylated hemoglobin (HbA1c), BP, and cholesterol in individuals with type 2 diabetes mellitus,[11–15] but it is uncertain whether the relationships between mortality and these cardiovascular risk factors in younger individuals can be applied to very old adults with diabetes mellitus because evidence is limited and results are inconclusive.[12,16–18] This study aimed to provide new evidence by testing the hypothesis that lower HbA1c, BP, and total cholesterol (TC) are associated with lower risk of all-cause mortality in very old adults with type 2 diabetes mellitus.

METHODS

Data Source

This study was conducted using the U.K. Clinical Practice Research Datalink (CPRD), which contains anonymized longitudinal electronic health records of 5.7 million active individuals from 680 general practices across the United Kingdom.[19] Data on prescriptions and diagnoses in the CPRD have been shown to be valid.[20] Results of physical examinations and biochemical tests are also recorded. The CPRD Independent Scientific Advisory Committee approved this study (ISAC Protocol 14_053).

Study Design and Participants

A population-based cohort study was designed including people aged 80 and older with type 2 diabetes mellitus as of January 1, 2012 (index date). Individuals were included if they contributed data between January 1 and December 31, 2011 (baseline). The date of diagnosis of diabetes mellitus was defined as the first diagnosis of diabetes mellitus, including HbA1c of ≥6.5% (≥48 mmol/mol), or first prescription of antidiabetic drugs. Prevalent diabetes mellitus was further confirmed during the baseline period based on diagnosis, prescription of antidiabetic drugs, and mean HbA1c. Individuals were excluded if they were diagnosed with type 1 or other specific types of diabetes mellitus, were first diagnosed with diabetes mellitus before the age of 30, or had been prescribed insulin within 180 days of the date of diagnosis. The details of study cohort selection are illustrated in Figure S1.

Measurement

Records for smoking status, body mass index (BMI), HbA1c, BP, and TC were evaluated during the 12-month baseline period. Smoking status and BMI were carried forward or carried back from data before or after baseline if participants did not have valid data in the baseline period. When participants had two or more valid values in the baseline period, mean values were used for analyses. Prescribed medicines were also evaluated for antidiabetic and cardiovascular drugs, including antihypertensive, lipid-lowering, oral antiplatelet, and oral anticoagulant drugs. Number of physician visits was counted in the baseline period as a proxy for intensity of observation. Comorbidities were analyzed using clinical records for coronary heart disease (CHD) and stroke. Age, sex, and duration of diabetes mellitus were measured at the index date. Deaths were ascertained from CPRD records. Records were censored when participants' CPRD records ended.

Analysis

Baseline characteristics of the study cohort were described, including age, sex, duration of diabetes mellitus, smoking status, BMI, frequency of physician visits, comorbidities, and medications. Time-to-event analyses were conducted from the end of the baseline period to earliest of death, date of transferred out of the practice, or December 31, 2013. Mortality (per 1,000 person-years) was calculated.

Associations between HbA1c, BP, and TC and all-cause mortality were estimated as unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) from Cox proportional hazards models. HRs were estimated for HbA1c categories of <6.0%, 6.0% to 6.4%, 6.5% to 6.9%, 7.0% to 7.4%, 7.5% to 7.9%, ≥8.5%, and missing and compared with 8.0% to 8.4% as reference (<42, 42–47, 48–52, 53–57, 58–63, ≥69 mmol/mol, and missing vs 64–68 mmol/mol); systolic BP/diastolic BP categories of <130/70, <135/75, <140/80, <145/85, <155/95, ≥155/95 mmHg, and missing and compared with <150/90 mmHg as reference; and TC categories of less than 3.0, 3.0 to 3.4, 3.5 to 3.9, 4.0 to 4.4, 5.0 to 5.4, ≥5.5 mmol/L, and missing and compared with 4.5 to 4.9 mmol/L as reference. The reference categories were selected according to the relaxed treatment targets for older adults with diabetes mellitus.[6] The relationships between HbA1c, BP, and TC and mortality were visualized using two-way quadratic prediction plots.

Four adjusted Cox models were constructed to evaluate the associations between HbA1c, BP, and TC and mortality adjusted for age and sex (Model 1); adjusted for age, sex, duration of diabetes mellitus (<5, 5–9, 10–14, ≥15 years), and prescription of antidiabetic drugs (Model 2); adjusted for age, sex, duration of diabetes mellitus, HbA1c, BP, TC (categorized as described above), and prescription of antidiabetic and cardiovascular drugs (Model 3); and age, sex, duration of diabetes mellitus, HbA1c, BP, TC, prescription of antidiabetic and cardiovascular drugs, smoking status (never, former, current), BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0 kg/m^2, missing), previous diagnoses of CVD (CHD or stroke), frequency of physician visits (<10, 10–19, 20–29, ≥30 per year), and clustering according to general practice (Final model). The proportional hazards assumption was assessed using Schoenfeld residuals and by inspecting log-log plots, and all covariates were retained in the models without adjustment.

Interactions between HbA1c, BP, or TC and sex; prescription of antidiabetic, antihypertensive, or lipid-lowering drugs, respectively; or a previous history of cardiovascular events were tested. Stratified analyses were conducted according to the effect modifiers identified. To address the question of reverse causality, the analysis was conducted after excluding participants who died in the first 6 months of follow-up. Thus, low HbA1c, BP, and TC may result from poor health status, which might also influence the intensity of diabetes management. In addition, the main analysis was repeated to identify high-risk categories of HbA1c, BP, and TC for all-cause mortality, with the

lowest-risk categories in the main analysis as reference, and the number of different high-risk categories was evaluated. All analyses were performed using Stata version 13 (Stata Corp., College Station, TX).

RESULTS

Baseline Characteristics

Baseline characteristics of participants, including comorbidities and medications, are shown in Table 1. The cohort comprised 25,966 participants, with 53% women, 90% aged 80 to 89 years, and 48% having had diabetes mellitus for longer than 10 years. A previous diagnosis of CHD was recorded in 35% of participants and of stroke in 11%. Eighty-four percent of participants were prescribed antidiabetic medications, and the most frequently prescribed antidiabetic drug was metformin (n = 15,720, 61%), followed by sulphonylureas (n = 10,930, 42%) and insulin (n = 3,436, 13%). Eighty-six percent of participants were prescribed antihypertensive drugs, and 70% received renin-angiotensin system blockers (n = 18,296). Lipid-lowering drugs, predominantly statins, were also frequently prescribed (77%). Fifty-five percent of participants received antiplatelet medications, and 12% received anticoagulants.

Table 1. Baseline Characteristics of the Study Population (N = 25,966)

Characteristic	n (%)
Age	
80–84	16,643 (64)
85–89	6,803 (26)
90–94	2,103 (8)
≥95	417 (2)
Sex	
Male	12,143 (47)
Female	13,823 (53)
Duration of diabetes mellitus, years	
<5	4,713 (18)
5–9	8,762 (34)
10–14	6,359 (24)
≥15	6,132 (24)
Smoking status[a]	
Never	13,672 (53)
Former	9,796 (38)
Current	2,498 (10)
Body mass index, kg/m^2[a]	
<18.5	288 (1)
18.5–24.9	6,313 (24)
25.0–29.9	9,520 (37)
≥30.0	7,299 (28)
Missing	2,546 (10)
Number of physician visits in past 12 months	
<10	3,355 (13)
10–19	9,469 (36)
20–29	6,535 (25)
≥30	6,607 (25)
Comorbidities	
Coronary heart disease	9,184 (35)
Stroke	2,788 (11)
Medications (past 12 months)	
Antidiabetic drugs	21,827 (84)
Antihypertensive drugs	22,456 (86)
Lipid-lowering drugs	20,102 (77)
Antiplatelets	14,297 (55)
Anticoagulants	3,170 (12)

[a]Figures are carried forward or carried back from data before or after baseline.

Pharmacological Treatment According to Category

Pharmacological treatment is shown according to HbA1c, BP, and TC categories in Table 2. In this cross-sectional observation, in the baseline period, the majority of participants were treated with antidiabetic, antihypertensive, and lipid-lowering drugs. Participants with higher HbA1c were more frequently prescribed antidiabetic drugs, and those with higher BP were more frequently prescribed antihypertensive drugs. Most participants with low TC levels and approximately half of those with high TC levels received lipid-lowering drugs. Two-thirds of participants with missing HbA1c, BP, or TC values during the 12-month baseline period were under antidiabetic, antihypertensive, or lipid-lowering medications.

Mortality

There were 4,490 deaths (17.3%, 104.7 per 1,000 person-years) in the follow-up period (median 2.0 years; 42,885

Table 2. Pharmacological Treatment According to Glycosylated Hemoglobin (HbA1c), Blood Pressure, and Total Cholesterol Categories

Factor	N	Treated, n (%)
Antidiabetic drugs according to HbA1c category, % (mmol/mol)		
<6.0 (<42)	1,387	1,387 (100)[a]
6.0–6.4 (42–47)	2,976	2,976 (100)[a]
6.5–6.9 (48–52)	7,463	5,057 (68)
7.0–7.4 (53–57)	4,700	3,915 (83)
7.5–7.9 (58–63)	2,777	2,548 (92)
8.0–8.4 (64–68)	1,780	1,698 (95)
≥8.5 (≥69)	3,006	2,950 (98)
Missing	1,877	1,296 (69)
Antihypertensive drugs according to blood pressure category, mmHg		
<130/70	4,116	3,519 (89)
≥130/70 & <135/75	4,416	3,742 (85)
≥135/75 & <140/80	4,749	4,102 (86)
≥140/80 & <145/85	4,746	4,129 (87)
≥145/85 & <150/90	2,534	2,251 (89)
≥150/90 & <155/95	1,717	1,553 (90)
≥155/95	2,663	2,466 (93)
Missing	1,025	694 (68)
Lipid-lowering drugs according to total cholesterol category, mmol/L		
<3.0	2,033	1,928 (95)
3.0–3.4	3,857	3,592 (93)
3.5–3.9	5,247	4,624 (88)
4.0–4.4	4,666	3,741 (80)
4.5–4.9	3,158	2,155 (68)
5.0–5.4	1,822	1,026 (56)
≥5.5	2,288	1,137 (50)
Missing	2,895	1,899 (66)

[a]Individuals with mean HbA1c <6.5% (<48 mmol/mol) and no prescription of antidiabetic drugs in the baseline period were excluded from the study cohort.

Table 3. Associations Between Glycosylated Hemoglobin (HbA1c), Blood Pressure, and Total Cholesterol and All-Cause Mortality (N = 25,966)

Factor	Deaths, n/N	%	Mortality (1,000 Person-Years)	Unadjusted	Adjusted
				Hazard Ratio (95% Confidence Interval) *P*-Value	
HbA1c, % (mmol/mol)					
<6.0 (<42)	301/1,387	21.7	134.9	1.21 (1.03–1.42) .02	1.04 (0.88–1.23) .67
6.0–6.4 (42–47)	506/2,976	17.0	102.1	0.92 (0.80–1.05) .21	0.91 (0.79–1.05) .19
6.5–6.9 (48–52)	1,081/7,463	14.5	85.6	0.77 (0.68–0.87) <.001	0.84 (0.74–0.96) .009
7.0–7.4 (53–57)	648/4,700	13.8	80.9	0.72 (0.63–0.83) <.001	0.80 (0.70–0.91) .001
7.5–7.9 (58–63)	453/2,777	16.3	98.6	0.88 (0.77–1.02) .09	0.90 (0.79–1.04) .15
8.0–8.4 (64–68)	324/1,780	18.2	111.5	Reference	Reference
≥8.5 (≥69)	641/3,006	21.3	133.1	1.20 (1.05–1.37) .009	1.04 (0.91–1.19) .55
Missing	536/1,877	28.6	195.9	1.76 (1.53–2.02) <.001	1.01 (0.86–1.19) .88
Blood pressure, mmHg					
<130/70	982/4,116	23.9	151.7	1.89 (1.67–2.13) <.001	1.52 (1.34–1.72) <.001
≥130/70 & <135/75	815/4,416	18.5	112.3	1.40 (1.23–1.58) <.001	1.30 (1.14–1.48) <.001
≥135/75 & <140/80	719/4,749	15.1	90.3	1.12 (0.99–1.27) .08	1.11 (0.97–1.27) .13
≥140/80 & <145/85	685/4,746	14.4	85.6	1.06 (0.93–1.21) .35	1.09 (0.95–1.24) .23
≥145/85 & <150/90	349/2,534	13.8	80.5	Reference	Reference
≥150/90 & <155/95	231/1,717	13.5	80.3	1.00 (0.85–1.18) .98	0.97 (0.82–1.14) .70
≥155/95	419/2,663	15.7	94.0	1.17 (1.01–1.35) .03	1.05 (0.91–1.22) .49
Missing	290/1,025	28.3	191.2	2.38 (2.04–2.78) <.001	1.38 (1.18–1.61) <.001
Total cholesterol, mmol/L					
<3.0	455/2,033	22.4	138.7	1.58 (1.39–1.80) <.001	1.42 (1.24–1.64) <.001
3.0–3.4	630/3,857	16.3	97.6	1.11 (0.99–1.25) .08	1.15 (1.02–1.29) .02
3.5–3.9	787/5,247	15.0	89.2	1.02 (0.91–1.14) .78	1.08 (0.96–1.21) .20
4.0–4.4	728/4,666	15.6	92.9	1.06 (0.94–1.19) .33	1.16 (1.03–1.30) .01
4.5–4.9	468/3,158	14.8	87.7	Reference	Reference
5.0–5.4	276/1,822	15.1	90.6	1.03 (0.89–1.20) .67	1.00 (0.85–1.16) .96
≥5.5	347/2,288	15.2	91.4	1.04 (0.91–1.20) .56	0.99 (0.86–1.13) .85
Missing	799/2,895	27.6	185.9	2.12 (1.89–2.38) <.001	1.40 (1.22–1.60) <.001

person-years). The distribution of deaths according to HbA1c, BP, and TC categories and unadjusted and fully adjusted HRs are shown in Table 3. Cox models adjusted for a range of covariates and HRs are shown in Table S1. A U-shaped relationship between HbA1c and mortality was observed (Figure S2). Mortality was 111.5 per 1,000 person-years in participants with the reference HbA1c category (8.0–8.4%, 64–68 mmol/mol). Mortality in participants with low (<6.0%, <42 mmol/mol) or high (≥8.5%, ≥69 mmol/mol) HbA1c was similar to that in those with the reference HbA1c category. Mortality in participants with baseline HbA1c of 7.0% to 7.4% (53–57 mmol/mol) was lowest (80.9 per 1,000 person-years, adjusted HR (aHR)=0.80, 95% CI=0.70–0.91, $P = .001$).

There appeared to be a reverse J-shaped relationship between BP and mortality (Figure S2). Mortality was 80.5 per 1,000 person-year in participants with the reference BP category (<150/90 mmHg). Mortality was 151.7 per 1,000 person-years in participants in the lowest BP category (<130/70 mmHg) (aHR = 1.52, 95% CI = 1.34–1.72, $P < .001$) and 112.3 per 1,000 person-years in participants in the second lowest BP category (<135/75 mmHg) (aHR=1.30, 95% CI=1.14–1.48, $P < .001$). Missing BP was also associated with higher mortality (aHR = 1.38, 95% CI=1.18–1.61, $P < .001$).

A decreasing trend of mortality was observed as baseline TC increased (Figure S2). Mortality was 87.7 per 1,000 person-years in participants with the reference TC category (4.5–4.9 mmol/L). Mortality of participants with the lowest TC category (<3.0 mmol/L) was highest (138.7 per 1,000 person-years, aHR=1.42, 95% CI = 1.24–1.64, $P < .001$). Missing TC was also associated with higher mortality (aHR = 1.40, 95% CI = 1.22–1.60, $P < .001$).

Sensitivity Analyses

There was evidence that the association between TC and mortality varied according to sex (P for interaction = .006) and prescription of lipid-lowering drugs (P for interaction = .001) (Table S2). Higher risk of mortality for low TC was more evident in women (e.g., for TC <3.0 mmol/L, aHR = 1.21, 95% CI = 1.01–1.46, $P = .04$ in men; aHR = 1.80, 95% CI = 1.46–2.22, $P < .001$ in women). TC level associated with higher mortality was <4.5 mmol/L in participants who were not prescribed lipid-lowering drugs (e.g., for TC 4.0–4.4 mmol/L, aHR = 1.38, 95% CI = 1.12–1.69, $P = .003$) but <3.0 mmol/L in participants prescribed lipid-lowering drugs (aHR = 1.33, 95% CI = 1.14–1.56, $P < .001$). The relationships between HbA1c, BP, and TC and mortality in the main analysis were retained after excluding participants who died in the first 6 months of follow-up (Table S3).

Combined Effects of High-Risk Categories

Based on the analysis with the lowest risk categories as reference, HbA1c less than 6.0% (<42 mmol/mol) or ≥8.0% (≥64 mmol/mol), BP less than 135/75 mmHg, and TC <3.0 mmol/L for men and <4.5 mmol/L for women were identified as the high-risk categories for mortality.

Mortality risk according to combinations of HbA1c, BP, and TC risk categories is shown in Table 4. Of participants included in this analysis (N = 22,248), 6,940 (31%) had lower risk categories for all three factors (mortality 69.3 per 1,000 person-years). Mortality was 93.9 per 1,000 person-years (aHR = 1.34, 95% CI = 1.23 to 1.47, $P < .001$) in participants with one high-risk category (n = 9,862, 44%); 120.4 per 1,000 person-years (aHR = 1.71, 95% CI = 1.55–1.90, $P < .001$) in participants with two high-risk categories (n = 4,686, 21%); and 156.9 per 1,000 person-years (aHR = 2.08, 95% CI = 1.76–2.44, $P < .001$) in participants with three high-risk categories (n = 760, 3%).

DISCUSSION

Main Findings

Relationships between HbA1c, BP, and TC and all-cause mortality were investigated in a large population-based sample of very old adults with type 2 diabetes mellitus. Low (<6.0%, <42 mmol/mol) or high (≥8.0%, ≥64 mmol/mol) HbA1c and low BP (<135/75 mmHg) and TC (<3.0 mmol/L) were associated with greater mortality, but causal relationships were not established between the high-risk ranges of these cardiovascular risk factors and mortality because of the observational nature of this study.

Greater risk of microvascular and cardiovascular complications could explain the association between high HbA1c and mortality.[13,21] Hypoglycemia might partly explain the association between low HbA1c and greater mortality, but the retrospective analysis of the ACCORD study suggested that severe hypoglycemia could not explain the greater risk of mortality in the intensive treatment group.[22] The current study adjusted for several covariates in the analyses, but the possibility of confounding cannot be completely excluded. Unmeasured confounding factors such as frailty, physical activity, and proteinuria might modify the associations between HbA1c, BP, and TC and mortality.[23–25] Confounding by indication might also arise if therapeutic interventions are reduced or increased in individuals approaching the end of life. Participants with missing values for BP and TC had greater risk of mortality, which indicates that physicians may be less likely to test individuals who are reaching the end of their lives. If individuals with worse conditions have low HbA1c, BP, and TC, reverse causality may explain the associations between the risk factors and mortality, which is potentially problematic in studies on mortality in older people with short follow-up. In the current study cohort, because the associations between low HbA1c, BP, and TC and greater mortality were retained in the analysis of participants after excluding those who died in the first 6 months of follow-up, reverse causation might not completely explain the associations. Further research on underlying mechanisms of the association between HbA1c, BP, and TC and mortality is needed, which could also inform individualized management of this heterogeneous population.

The associations between low HbA1c, BP, and TC and higher mortality have been reported in previous observational studies. A recent study with the CPRD demonstrated that HbA1c of 7.25% to 7.75% (56–61 mmol/mol), systolic BP of 135 to 145 mmHg, diastolic BP of 82.5 to 87.5 mmHg, and TC of 3.5 to 4.5 mmol/L were associated with the lowest risk of mortality in individuals with type 2 diabetes mellitus with a mean age of

Table 4. Mortality Risk According to Combinations of Glycosylated Hemoglobin (HbA1c), Blood Pressure, and Total Cholesterol Risk Categories (N = 22,248)

Number of High Risk Categories	HbA1c, %	Blood Pressure, mmHg	Total Cholesterol, mmol/L	Deaths, n/N	%	Mortality (1,000 Person-Years)	Adjusted Hazard Ratio (95% Confidence Interval)	*P*-Value
0	–	–	–	830/6,940	12.0	69.3	Reference	
1	<6.0	–	–	59/429	13.8	82.1	0.98 (0.75–1.28)	.89
	≥8.0	–	–	302/1,884	16.0	96.6	1.28 (1.12–1.46)	<.001
	–	<135/75	–	631/3,478	18.1	109.5	1.37 (1.23–1.52)	<.001
	–	–	Men <3.0, Women <4.5	556/4,071	13.7	80.8	1.41 (1.25–1.58)	<.001
2	<6.0	<135/75	–	79/263	30.0	199.3	2.29 (1.79–2.92)	<.001
	<6.0	–	Men <3.0, Women <4.5	58/318	18.2	109.9	1.62 (1.23–2.13)	.001
	≥8.0	<135/75	–	212/856	24.8	159.6	1.77 (1.51–2.08)	<.001
	≥8.0	–	Men <3.0, Women <4.5	188/1,021	18.4	111.5	1.60 (1.35–1.89)	<.001
	–	<135/75	Men <3.0, Women <4.5	382/2,228	17.1	103.4	1.66 (1.45–1.90)	<.001
3	<6.0	<135/75	Men <3.0, Women <4.5	59/229	25.8	160.7	2.09 (1.59–2.75)	<.001
	≥8.0	<135/75	Men <3.0, Women <4.5	130/531	24.5	155.2	2.06 (1.68–2.53)	<.001

Participants with missing values for HbA1c, blood pressure, or total cholesterol were excluded from the analysis (n = 3,718).
Low risk for mortality: HbA1c 6.0–7.9% (42–63 mmol/mol); blood pressure ≥135/75 mmHg; total cholesterol ≥3.0 mmol/L for men and ≥4.5 mmol/L for women.

66.[13] The relationship between HbA1c and mortality observed in that study was similar to that found in the current study, but this study suggests a higher optimal range for BP and TC. Higher percentages of women in the study cohort might have partly caused the difference in the relationship between TC and mortality. The current results were generally in line with findings from previous studies in older adults. HbA1c of 6.0% to 7.9% (42–63 mmol/mol) were associated with lower risk of mortality in individuals aged 80 and older with diabetes mellitus,[16] which was consist with the lower risk range based on the present study. The association between low BP and higher mortality was observed in individuals with type 2 diabetes mellitus and renal impairment (mean age 75)[18] and in individuals aged 80 and older, including 25% of participants with diabetes mellitus.[26] It was shown that TC of <5.5 mmol/L tended to be associated with higher mortality, with the lowest at approximately 6 mmol/L in participants aged 80 and older.[27]

Evaluation of appropriateness of drug use would be the next step for better management. Frequent prescribing of antidiabetic and cardiovascular drugs has been found in very old adults who were newly diagnosed with type 2 diabetes mellitus.[28] A recent study in the United States suggested possible overtreatment with antidiabetic drugs in older adults with diabetes mellitus, especially those treated with insulin or sulphonylureas, which may cause severe hypoglycemia.[29] A meta-analysis of randomized controlled trials indicated that antihypertensive medications reduced the risk of CVD but did not reduce mortality in participants aged 80 and older.[30] Use of lipid-lowering drugs should be individualized because of the biological heterogeneity of people aged 80 and older.[31] The majority of participants with low HbA1c, BP, and TC in the current study cohort were under treatment with antidiabetic, antihypertensive, and lipid-lowering drugs, respectively, which may suggest possible overtreatment in primary care in the United Kingdom. More evidence is needed for informed decision-making to initiate or discontinue these medications for very old adults with diabetes mellitus.

Strengths and Limitations

A strength of the present study was the inclusion of a large, representative sample of general population in primary care across the United Kingdom. Given that it has been difficult to include very old people in clinical trials because of safety reasons, the findings are considered complementary and of importance in drawing attention to the possible negative associations between low HbA1c, BP, and TC and survival in very old people with diabetes mellitus.

There are also some limitations of the study. First, longer follow-up could reach other conclusions because individuals with a longer life expectancy may be expected to obtain health benefits from tight control of cardiovascular risk factors.[6] Second, HbA1c, BP, and TC values from the 12-month baseline period were included in the analyses, but these variables might fluctuate over time, and long-term management might affect clinical outcomes. Third, cause of death, which is not immediately available in the CPRD, was not analyzed. Additional information on cause of death would aid interpretation of the present study results. Fourth, an individual's age may directly inform treatment recommendations, but stratified evaluation of individuals according to frailty and other characteristics might be more important because of the heterogeneity of older adults.[6] Finally, there were some limitations commonly intrinsic to retrospective studies with electronic health records. The analyses depended on completeness and accuracy of CPRD records. Information was not available on whether participants actually took medications prescribed. Many of these limitations could be overcome through the conduct of randomized controlled trials, but these have yet to be reported for very old people with type 2 diabetes mellitus.

CONCLUSION

The present study demonstrated that low HbA1c, BP, and TC might be associated with higher mortality in very old adults with type 2 diabetes mellitus. These observational data may suggest that stringent targets for the cardiovascular risk factor reduction are not always optimal in this population. Additional research is required to understand these associations observed in this study and to identify optimal HbA1c, BP, and TC during therapeutic intervention for vulnerable old people at possible high risk of CVD.

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Author Contributions: Both authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Both authors: study concept and design, analysis and interpretation of data, drafting the article, revising it critically for intellectual content, approval of final version to be published. Gulliford: acquisition of data.

Sponsor's Role: This study is based on data from the CPRD obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The interpretation and conclusions contained in this report are those of the authors alone and not necessarily those of the National Health Service, the NIHR or the Department of Health.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow Diagram of Study Cohort.

Figure S2. Relationship Between Glycosylated Hemoglobin (HbA1c), Blood Pressure, and Total Cholesterol and Mortality.

Table S1. Cox Models.

Table S2. Analyses Stratified According to Effect Modifiers.

Table S3. Analysis After Excluding Participants Who Died in the First 6 Months of Follow-Up.

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